



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : ZHI *et al.*  
Serial No. : 10/589,920  
Filed : April 20, 2007  
Title : **GLUCOCORTICOID RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1614  
Examiner : Thomas, Timothy P.  
Confirm. No.: 3750

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION PURSUANT TO 37 C.F.R. §1.132**

Sir:

I, **Lin Zhi**, declare as follows,

1) I am an inventor of the above-captioned application, which is the National Stage of International Application. No. PCT/US2005/06627, filed February 24, 2005, which claims benefit of priority to U. S. provisional patent application Serial No. 60/548,154, filed February 25, 2004.

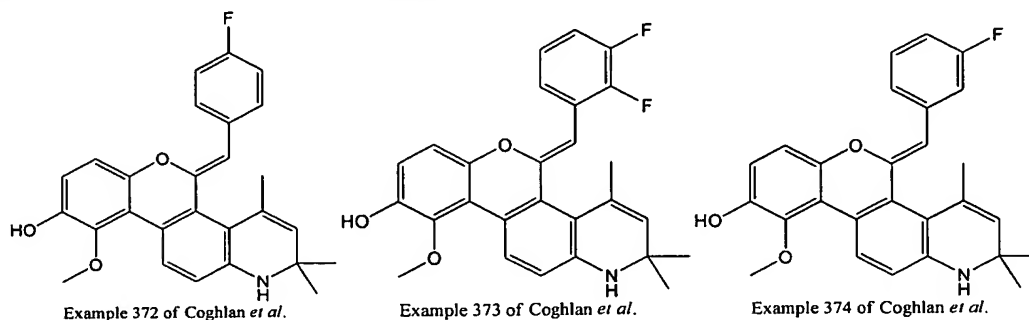
2) I obtained my B.S. and M.S. in chemistry from Beijing University in China. I obtained my Ph.D. in synthetic organic chemistry in 1990 from Emory University under the supervision of Prof. Albert Padwa. After postdoctoral training with Prof. Barry Trost in Stanford University, I joined Ligand Pharmaceuticals Inc. in 1992. I work in the area of small-molecule drug discovery targeted at intracellular/nuclear receptors. Currently, I hold the Senior Director position in Chemistry and Pharmaceutical Science at Ligand Pharmaceuticals Inc. I have over 60 publications and 60 issued US patents.

3) I have reviewed the Office Action, mailed August 25, 2008, in connection with the above-captioned application.

4) The above-captioned application provides selective glucocorticoid receptor modulator compounds and selective glucocorticoid receptor binding compounds. The compounds described in the above-captioned application interact with the glucocorticoid receptor to alter its activity.

5) The Office Action cites Coghlan *et al.* (International Patent Application PCT/01/20423, which published as WO02/02565). I have reviewed the disclosure of Coghlan *et al.* This reference describes 445 compounds. I have reviewed these compounds and compared these compounds to the compounds of the above-captioned application which are set forth as formula I in claim 1. Three of the compounds of Coghlan *et al.* are

structurally similar to the compounds claimed in the above-captioned application. The structurally related compounds are the compounds described in Examples 372-374 of Coghlan *et al.*, and have the following structures:



The compound described in Example 372 of Coghlan *et al.* is structurally similar to the compound described in Example 9 of the above-captioned application, but the compound described in Example 9 has a methyl group at position 4 of the pendent phenyl ring instead of a F atom. The compound described in Example 373 of Coghlan *et al.* is structurally similar to the compound described in Example 18 of the above-captioned application, but the compound of Example 18 has a methyl group at position 3 of the pendent phenyl ring instead of a F atom. The compound described in Example 374 of Coghlan *et al.* is structurally similar to the compound described in Example 8 of the above-captioned application, but the compound of Example 8 has a methyl group at position 3 of the pendent phenyl ring instead of a F atom. Thus, these compounds represent the closest compounds to those of formula I of claim 1.

6) The ability of a compound to modulate the transcriptional ability of intracellular receptors, including glucocorticoid receptors, can be measured by any of the assays known in the art. The specification teaches how to identify compounds of formula I that are agonists or antagonists of the glucocorticoid receptor and compounds that bind to the glucocorticoid receptor. For example, Example 235 teaches a receptor binding assay to assess whether a compounds binding to the glucocorticoid receptor (see pages 270-272). The Example provides a detailed description of the co-transfection assay and the receptor binding assay.

7) The activity of each of the compounds described in Examples 372 and 373 of Coghlan *et al.* was assessed. I compared the activity of the compounds of Examples 372 and 373 of Coghlan *et al.* to their structural analogs described in the above-captioned application. I used the competitive binding assay described in the above-captioned application to determine the glucocorticoid receptor (GR) binding activity of each of compounds of Examples 9 and 18 of the above-captioned application and its structural analog (the compound described in Examples 372 and 373 of Coghlan *et al.*, respectively). I also determined the glucocorticoid

receptor (GR) binding activity of the compound described in Example 8 of the above-captioned application. In order to determine the progesterone receptor (PR) binding activity of the compounds, I used the GR assay as described in the application but replaced the GR lysate and [<sup>3</sup>H]dexamethasone with PR lysate and [<sup>3</sup>H]progesterone. A description of the assays and the results of the assays are provided in the following sections.

8) As discussed below, each of the compounds of Examples 9 and 18 of the above-captioned application demonstrate significantly improved receptor selectivity between the glucocorticoid receptor and the progesterone receptor compared to their closest structural analogs described in the examples of Coghlan *et al.* The compound of Example 8 of the above-captioned application also demonstrates an improved GR/PR receptor selectivity when compared to the values of the compounds of Examples 372 and 373 of Coghlan *et al.* Thus, it can be inferred that the compounds of formula I of claim 1 of the above-captioned application exhibit improved receptor selectivity compared to the compounds of Coghlan *et al.*

#### A. Assay Description

Binding assay samples were prepared in separate mini-tubes in a 96-well format at 4 °C. Each binding assay sample was prepared in a volume of 250 µL. For the GR binding assay, each assay sample was prepared in a volume of 250 µL of Assay Buffer (10% glycerol, 25 mM sodium phosphate, 10 mM potassium fluoride, 10 mM sodium molybdate, 0.25 mM CHAPS, 2 mM DTT and 1 mM EDTA, (adjusted to pH 7.5)) containing 50 µg of GR lysate; 2-4 nM of [<sup>3</sup>H]dexamethasone at 84 Ci/mmol; and either a reference compound or a test compound. For the PR binding assay, each assay sample was prepared in a volume of 250 µL of Assay Buffer (10% glycerol, 25 mM sodium phosphate, 10 mM potassium fluoride, 10 mM sodium molybdate, 0.25 mM CHAPS, 2 mM DTT and 1 mM EDTA, (adjusted to pH 7.5)) containing 50 µg of PR lysate; 2-4 nM of [<sup>3</sup>H]progesterone at 97-102 Ci/mmol; and either a reference compound or a test compound.

Test compounds included selective glucocorticoid binding compounds 9 and 18 of the above-captioned application and structurally similar analogs described in Coghlan *et al.* (compounds described in Examples 372 and 373, respectively). The compound of Example Reference compounds for the GR receptor were unlabeled dexamethasone and prednisone, which previously have been shown to bind to glucocorticoid receptors. The reference compound for the PR receptor was unlabeled progesterone. Each reference compound and test compound was assayed at varying concentrations, ranging from 0 to 10<sup>-5</sup> M. Each concentration of each reference compound and each test compound was assayed in triplicate. The assay samples were incubated for 16 hours at 4 °C.

After incubation, 200  $\mu$ L of 6.25% hydroxylapatite in assay buffer was added to each assay sample to precipitate the protein. The assay samples then were centrifuged and the supernatants were discarded. The resulting pellets were washed twice with assay buffer that did not include any DTT. Radioactivity in counts per minute (CPM) of each washed pellet was determined using a liquid scintillation counter.

Specific binding for each sample was calculated using the equation:

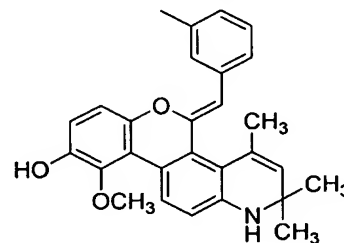
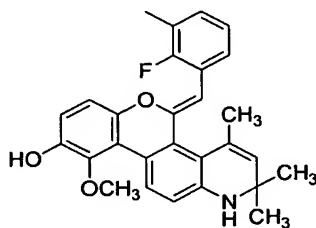
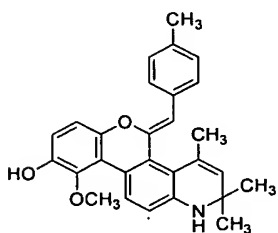
$$(\text{Sample CPM}) - (\text{Average Non-specific CPM})$$

"Average Non-specific CPM" was defined as the amount of radioactivity from samples containing an excess (*i.e.* 1000 nM) of unlabeled dexamethasone.  $IC_{50}$  values (the concentration of test compound required to decrease specific binding by 50%) were determined using the log-logit (Hill) method.  $K_i$  values were determined using the Cheng-Prusoff equation using a previously determined  $K_d$  value for dexamethasone:

$$K_i = IC_{50} / (1 + [L] / K_d)$$

where  $[L]$  is the concentration of labeled dexamethasone and  $K_d$  is the dissociation constant of labeled dexamethasone.

9) I tested the closest structural analogs of the compounds of formula I of claim 1 of the above-captioned application of the compounds described in Coghlan *et al.* These included compounds of Examples 8, 9 and 18, the structures of which are shown below:



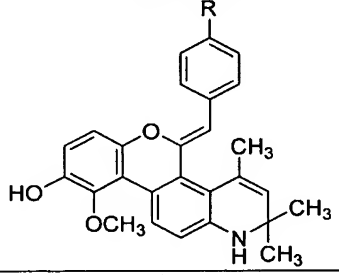
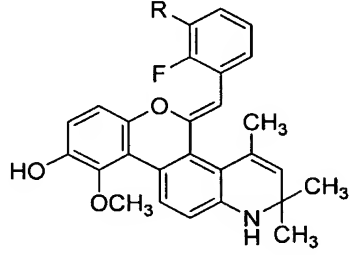
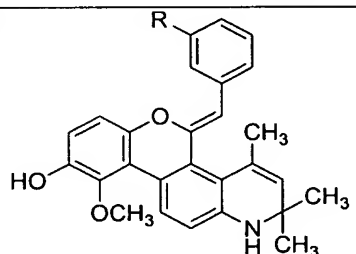
Example 9 of App. Ser. No. 10/589,920    Example 18 of Appl. Ser. No. 10/589,920    Example 8 of Appl. Ser. No. 10/589,920

I compared the compound described in Example 372 of Coghlan *et al.* to the compound described in Example 9 of the above-captioned application. The compounds differ in that the compound of Example 9 of the above-captioned application has a methyl group at position 4 of the pendent phenyl ring while the compound of Example 372 of Coghlan *et al.* has a F atom at position 4 of the pendent phenyl ring. I also compared the compound described in Example 373 of Coghlan *et al.* to the compound described in Example 18 of the above-captioned application. The compounds differ in that the compound of Example 18 of the above-captioned application has a fluorine atom at position 2 and a methyl group at position 3 of the pendent phenyl ring instead of a fluorine atom at positions 2 and 3 of the pendent phenyl ring. I also tested the compound described in Example 8 of the above-captioned

application. The compound of Example 8 of the above-captioned application has a methyl group at position 3 of the pendent phenyl ring.

The inhibitory potency and selectivity for GR and PR receptors of the compounds of the above-captioned application and their closest structural analogs described in Coghlan *et al.* are shown below:

#### Binding Assay Results

Structure	K <sub>i</sub> (nM)	
	WO 02/02565 (R = F)	US 10/589,920 (R = CH <sub>3</sub> )
	<b>Compound 372</b> GR Binding: 1.8 nM PR Binding: 164 nM GR/PR selectivity: 91	<b>Example 9</b> GR Binding: 1.9 nM PR Binding: 1394 nM (8.5-fold difference) GR/PR selectivity: 734 (8-fold difference)
	<b>Example 373</b> GR Binding: 3.1 nM PR Binding: 279 nM GR/PR selectivity: 90	<b>Example 18</b> GR Binding: 2.4 nM PR Binding: 893 nM (3-fold difference) GR/PR selectivity: 372 (4-fold difference)
	<b>Example 374</b> data not available	<b>Example 8</b> GR Binding: 2.5 nM PR Binding: 397 nM GR/PR selectivity: 159

10) The compound of the above-captioned application with a methyl group at position 4 (Example 9) had a PR binding of 1394 nM compound and its closest structural analog with a F atom at position 4 (Example 372 of Coghlan *et al.*) had a PR binding of 164 nM. Thus, the compound of the above-captioned application with a methyl group at position 4 instead of a F atom demonstrates a 8.5-fold decrease in PR binding compared to its closest structural analog (the compound of Example 372) of Coghlan *et al.*

In the assays measuring the receptor selectivity between GR and PR, the compound of Example 9 of the above-captioned application (having a methyl group at position 4 of the pendent phenyl ring) demonstrated consistently higher GR/PR selectivity than its analog described in Example 372 of Coghlan *et al.*, which has a F atom at position 4 of the pendent phenyl ring. The GR/PR selectivity of the compound of Coghlan *et al.* was 91-fold (1.8 nM

v. 164 nM) while the GR/PR selectivity of the compound of the above-captioned application having a methyl group at position 4 of the phenyl ring (Example 9) was 734-fold (1.9 nM v. 1394 nM). Thus, the compound of the above-captioned application with a methyl group at position 4 of the phenyl ring instead of a F atom demonstrated an 8-fold improvement in the GR/PR selectivity compared to its closest structural analog (the compound of Example 372 of Coghlan *et al.*).

11) The compound of the above-captioned application with a methyl group at position 3 of the pendent phenyl ring (compound of Example 18) had a PR binding of 893 nM and its structural analog with a F atom at position 3 of the pendent phenyl ring (the compound described in Example 373 of Coghlan *et al.*) had a PR binding of 279 nM. Thus, the compound of the above-captioned application with a methyl group at position 3 of the pendent phenyl ring instead of a F atom demonstrates a greater than 3-fold decrease in PR binding compared to its closest structural analog (the compound of Example 373 of Coghlan *et al.*).

In the assays measuring the receptor selectivity between GR and PR, the compound of Example 18 of the above-captioned application demonstrated consistently higher GR/PR selectivity than its analog described in Example 373 of Coghlan *et al.* The GR/PR selectivity of the compound of Example 373 of Coghlan *et al.* was 90-fold (3.1 nM v. 279 nM) while the GR/PR selectivity of the compound of Example 18 of the above-captioned application was 372-fold (2.4 nM v. 893 nM). Thus, the compound of the above-captioned application with a methyl group at position 3 of the phenyl ring instead of a F atom demonstrated a 4-fold improvement in the GR/PR selectivity compared to its closest structural analog (the compound of Example 373 of Coghlan *et al.*).

12) The compound of the above-captioned application with a methyl group at position 3 of the pendent phenyl ring (the compound of Example 8) a PR binding of 397 nM. The binding data for the structural analog of Coghlan *et al.* was not available. In the assays measuring the receptor selectivity between GR and PR, the compound of Example 8 of the above-captioned application had a GR/PR selectivity of 159-fold (2.5 nM v. 397 nM).

13) The compounds of formula I of claim 1 of the above-captioned application, which have a methyl group at position 4 of the phenyl ring instead of a F atom (Example 9) or a methyl group at position 3 of the phenyl ring instead of a F atom (Examples 8 and 18) demonstrate decreased PR binding and significantly improved GR/PR selectivity when compared to their closest structural analogs described in Coghlan *et al.* (e.g., compounds of Examples 372 and 373). Thus, compounds of formula I of claim 1 of the above-captioned

application have properties that differ from the closest structural analogs described in Coghlan *et al.*

14) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

2/25/09  
Date

  
Lin Zhi



Attorney's Docket No.: 18202-027US1/1110US

### DECLARATION FOR PATENT APPLICATION

As below-named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled

#### GLUCOCORTICOID RECEPTOR MODULATOR COMPOUNDS AND METHODS

the specification of which:

- ( ) is attached hereto.  
( ) was filed by an authorized person on my behalf on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_.  
(X) is PCT International Application No. PCT/US2005/006627 filed on 24 February 2004, and as amended in the Preliminary Amendment filed on August 17, 2006.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and so identified, or §365(a) of any PCT international application that designated at least one country other than the United States of America, listed below, and we have also identified below any foreign application for patent or inventor's certificate or PCT international application on this invention filed by us or by legal representatives or assigns and having a filing date before that of the application on which priority is claimed.

<u>Number</u>	<u>Country</u>	<u>Day/Month/Year Filed</u>	<u>Priority Claimed (Yes or No)</u>
N/A			

We hereby claim benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

<u>Application Serial No.</u>	<u>Filing Date</u>
60/548,154	25 February 2004



We hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
N/A		

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N/A		

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We hereby appoint the following attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith and request that all correspondence and telephone calls in respect to this application be directed to Stephanie Seidman, FISH & RICHARDSON P.C., 12390 El Camino Real, San Diego, California 92130-2081; (858) 678-5070:

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Scott C. Harris	32,030
Paula K. Schoeneck	39,362
Frank J. Miskiel	53,332

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#### GLUCOCORTICOID RECEPTOR MODULATOR COMPOUNDS AND METHODS

the specification of which:

- ( ) is attached hereto.
- ( ) was filed by an authorized person on my behalf on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_.
- (X) is PCT International Application No. PCT/US2005/006627 filed on 24 February 2004, and as amended in the Preliminary Amendment filed on August 17, 2006.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and so identified, or §365(a) of any PCT international application that designated at least one country other than the United States of America, listed below, and we have also identified below any foreign application for patent or inventor's certificate or PCT international application on this invention filed by us or by legal representatives or assigns and having a filing date before that of the application on which priority is claimed.

<u>Number</u>	<u>Country</u>	<u>Day/Month/Year Filed</u>	<u>Priority Claimed (Yes or No)</u>
N/A			

We hereby claim benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

<u>Application Serial No.</u>	<u>Filing Date</u>
60/548,154	25 February 2004

We hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
N/A		

<u>PCT Application No.</u>	<u>Filing Date</u>	<u>Status</u>
N/A		

We hereby declare that all statements made therein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

We hereby appoint the following attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith and request that all correspondence and telephone calls in respect to this application be directed to Stephanie Seidman, FISH & RICHARDSON P.C., 12390 El Camino Real, San Diego, California 92130-2081; (858) 678-5070:

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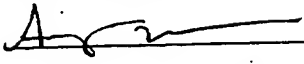
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